

Polymyalgia rheumatica

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Polymyalgia rheumatica is the most common inflammatory rheumatic disease in elderly white people, and it is a common indication for long term treatment with glucocorticosteroids in patients based in the community.^{1,2} Although the symptoms are very characteristic, several other autoimmune, infectious, endocrine, and malignant disorders can present with similar symptoms. The course of disease is heterogeneous and unpredictable, and giant cell arteritis is seen in about 30% of patients.³ Glucocorticosteroids rapidly improve disease symptoms in most patients but may have serious side effects. This review looks at the current understanding of diagnosis and the management of polymyalgia rheumatica.

Who is at risk of polymyalgia rheumatica?

Polymyalgia rheumatica is seen mainly in people of north European ancestry, although it can occur in any ethnic group. It is almost never seen in people under the age of 50, and its prevalence increases with increasing age. The average age of onset is just over 70, and 75% of patients are women. The incidence of the disease in patients over 50 is about 100 per 100 000.^{1,2}

What is the pathogenesis of polymyalgia rheumatica?

The cause of polymyalgia rheumatica is unknown, although both genetic and environmental factors contribute to disease susceptibility and severity. Some studies show a cyclical pattern in incidence, which suggests an environmental infectious trigger, such as parvovirus B19, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.⁴

Polymyalgia rheumatica has a modest familial aggregation. It is linked to the HLA DR4 allele in white populations. Epigenetic changes and differential expression of genes that regulate the expression of inflammatory cytokines probably account for the variable disease phenotypes.⁴

What are the clinical features of polymyalgia rheumatica?

The most characteristic presenting feature of polymyalgia rheumatica is bilateral shoulder pain and stiffness of acute or subacute onset with bilateral

upper arm tenderness. Patients often develop concomitant hip girdle pain and stiffness, as well as pain and stiffness in the posterior neck musculature.³ Muscle weakness is not a feature of the disease, although this can be difficult to assess in the presence of muscle pain; when symptoms are protracted and untreated, disuse atrophy can occur. Stiffness after periods of rest and morning stiffness of more than one hour are typical. The stiffness may be so profound that patients have great difficulty turning over in bed, rising from a bed or a chair, or raising their arms above shoulder height—for example, to comb their hair. Mild synovitis may be seen in the wrists and knees, but the feet and ankles are only rarely affected. Especially at the onset of the disease, most patients have systemic symptoms including fatigue, loss of appetite, weight loss, low grade fever, and sometimes depression. Patients are always over the age of 50 and usually over 65.

In patients who present with polymyalgic symptoms, remember that inflammatory rheumatic diseases that mimic polymyalgia rheumatica are more prevalent than polymyalgia rheumatica itself in people under 60. An erythrocyte sedimentation rate greater than 40 mm/h is a characteristic laboratory finding in polymyalgia rheumatica, but it may not be that high at presentation and can even be normal.⁵ Even in this setting, C reactive protein is usually raised.

How is polymyalgia rheumatica diagnosed?

Most of the evidence for the diagnosis and treatment of polymyalgia rheumatica comes from case series, expert opinion, and our own clinical experience, rather than randomised controlled trials. Guidelines recommend that the diagnosis of this disease is carried out in a stepwise manner (box 1; table).⁶ The first step is to assess the patient's symptoms including pain and

Sources and selection criteria

We searched PubMed, Embase, Scopus, Premedline, and National Institutes for Health Clinical Trials publications from 2000 to 2007 for strategies for the diagnosis and management of polymyalgia rheumatica. We found no Cochrane reviews on the subject.

Polymyalgia rheumatica: differential diagnosis and testing

| Diagnosis | Clinical features |
|--|--|
| Inflammatory disorders | |
| Polymyalgia rheumatica | Age >50 years, predominantly proximal shoulder and hip girdle symptoms, symmetrical; non-erosive joint disease on radiography |
| Rheumatoid arthritis | Mainly distal joint symptoms; positive for rheumatoid factor and anticyclic citrullinated peptide; erosive joint disease on radiography |
| Late onset spondyloarthropathy, including ankylosing spondylitis, psoriatic arthritis | Predominantly low back stiffness and pain; may have large and distal joint symptoms; spinal ankylosis on radiography; psoriasis |
| RS3PE (remitting seronegative symmetric synovitis with pitting oedema) syndrome | Peripheral hand or foot oedema |
| Systemic lupus erythematosus, scleroderma, Sjögren's syndrome, vasculitis | Fatigue, stiffness, multisystem disease; presence of antinuclear antibodies and antineutrophil cytoplasmic antibodies |
| Dermatomyositis, polymyositis | Proximal muscle weakness, rash; creatine kinase raised |
| Non-inflammatory disorders | |
| Osteoarthritis, spinal spondylosis | Articular pain of shoulder, neck, and hip joints; gelling; degenerative changes on radiography |
| Rotator cuff disease, adhesive capsulitis (frozen shoulder) | Periarticular pain, restricted range of motion; ultrasound and magnetic resonance imaging may show characteristic bursal and synovial inflammation |
| Infections, including viral syndromes, osteomyelitis, bacterial endocarditis, tuberculosis | Fever, weight loss, heart murmur, deep soft tissue and bone pain, microscopic haematuria |
| Cancer (lymphoma, leukaemia, myeloma, amyloidosis; occult solid tumours) | Weight loss, fatigue; investigations according to symptoms, sex, and age |
| Parkinsonism | Stiffness, rigidity, shuffling gait, gradual onset |
| Chronic pain syndromes, fibromyalgia, depression | Fatigue, longstanding pain, tender points, sadness, loss of usual interests |
| Endocrinopathy and metabolic bone disease: hyperthyroidism, hypothyroidism, hyperparathyroidism, hypoparathyroidism, hypovitaminosis D, osteomalacia, pseudogout with calcium pyrophosphate deposition | Bone pain, fatigue; abnormalities of parathyroid hormone, calcium, phosphorus, vitamin D concentrations, thyroid stimulating hormone |

stiffness in the shoulder or hip girdle (or both)—usually of at least one week's, and more confidently of at least two weeks', duration—in the presence of acute inflammatory markers, including erythrocyte sedimentation rate or C reactive protein. Patients must be assessed for the presence of giant cell arteritis, which is seen in about 30% of people with polymyalgia rheumatica.³⁴ Symptoms of giant cell arteritis include new headache, jaw claudication (jaw muscle pain on chewing), and visual disturbance. The temporal artery may be abnormal to palpation; biopsy of this artery usually yields characteristic findings of vascular inflammation. Such a biopsy should be considered in any patient with polymyalgic symptoms and new headache.

The presenting symptoms are non-specific and may reflect several other serious medical conditions.^{34,7} Clinicians should think of polymyalgia rheumatica as “polymyalgia syndrome” at first evaluation and should carefully assess whether another—possibly life threatening—illness could be underlying the symptom complex.

It is important to exclude other mainly inflammatory conditions that can mimic polymyalgia rheumatica. These include rheumatoid arthritis (often with negative rheumatoid factor or antibodies to cyclic citrullinated peptide) and less common conditions, such as late onset undifferentiated spondyloarthropathy, systemic lupus erythematosus, systemic vasculitis, and inflammatory myopathy (polymyositis, dermatomyositis).

These inflammatory conditions can be distinguished from non-inflammatory conditions, including infections—such as bacterial endocarditis, chronic osteomyelitis, viral syndromes, and tuberculosis—as well as

degenerative disorders, such as rotator cuff disorders and osteoarthritis. Other non-inflammatory conditions associated with proximal muscle stiffness include endocrine and metabolic diseases, such as thyroid and parathyroid disorders and osteomalacia. Depression; neurological disorders such as parkinsonism; malignancy; side effects of drugs—for example, myalgia caused by statins; and chronic pain conditions, including fibromyalgia, may be the eventual diagnosis in some cases of suspected polymyalgia syndrome (table).

Treatment with a moderate dose of prednisone—15 mg once daily in the morning—can help confirm the diagnosis.^{34,89} The dose can be increased to 20 mg a day, but patients should never be given a higher dose,

TIPS FOR NON-SPECIALISTS

Suspect polymyalgia rheumatica in patients over 65 who have subacute to acute onset of bilateral shoulder pain and stiffness

Measure acute phase reactants, such as C reactive protein, or the erythrocyte sedimentation rate, which are almost always raised at disease outset

Start treatment with glucocorticosteroids in the form of prednisone, 15–20 mg a day. This should greatly improve disease symptoms within one to three days

Patients may need several years of treatment

Non-steroidal anti-inflammatory agents are of little value for the management of this disease

Polymyalgia rheumatica may be associated with giant cell arteritis, and it is important to ask about symptoms and signs of this condition

which would only contribute to delays in diagnosis of another condition and lead to more morbidity as a result of treatment with corticosteroids. Often, within 24–48 hours patients will report, “it’s a miracle, doctor.” Within three to four weeks patients should report at least a 70% global improvement, and the erythrocyte sedimentation rate and C reactive protein value should normalise.⁸ If the initial response to treatment is not dramatic, treatment should not be continued without considering other diagnoses. The dose of prednisone should not be increased to try to lower persistently high concentrations of acute phase reactants. Lack of complete response to recommended doses of prednisone, as well as atypical clinical features (younger age, muscle weakness, peripheral joint disease, and predominance of pain with little or no stiffness), should lead to consideration of alternative diagnoses.

Ultrasonography has been proposed as an adjunct to the diagnosis of polymyalgia rheumatica.¹⁰ Ultrasound shows characteristic pathological findings of the shoulders and hips that can help distinguish polymyalgia rheumatica from other diseases. Typical findings on ultrasound include subdeltoid bursitis and biceps tendon tenosynovitis of the shoulders and, less frequently, synovitis of the glenohumeral joint. In the hips, ultrasound often reveals synovitis and trochanteric bursitis. Inflammatory shoulder lesions have been seen even in patients with normal erythrocyte sedimentation rates. Ultrasound may be particularly useful in patients with typical proximal symptoms of polymyalgia who have a normal erythrocyte sedimentation rate.

Other diagnostic tests, such as magnetic resonance imaging and bone and radionuclide labelled bone and joint scanning, have been used in case series to evaluate polymyalgia rheumatica, but their clinical usefulness has yet to be established.¹¹

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

American College of Rheumatology (www.rheumatology.org/educ/training/readinglist/index.asp)—Website containing information on rheumatological diseases, for physicians and patients

Up to Date (www.uptodate.com/)—Website designed to answer the clinical questions that arise in daily practice

MD Consult (www.mdconsult.com/php/82911852-3/homepage)—Website that brings the leading medical resources together into one integrated online service to help doctors answer clinical questions and make better treatment decisions

Resources for patients

American College of Rheumatology (www.rheumatology.org/public/factsheets/pmr_new2.asp)—Information for patients on polymyalgia rheumatica

Arthritis Foundation (www.arthritis.org/disease-center.php?disease_id=20)—Information and support for patients with arthritis and related conditions

Patient UK (www.patient.co.uk/showdoc/500/)—Information leaflet on polymyalgia rheumatica

Up to Date Patient Information (http://patients.uptodate.com/topic.asp?file=arth_rhe/5721)—Information on polymyalgia rheumatica and giant cell (temporal) arteritis

Arthritis Research Campaign (www.arc.org.uk/arthinfo/patpubs/6032/6032.asp)—Information leaflet on polymyalgia rheumatica and support

Box 1 Diagnosis and treatment of polymyalgia rheumatica

Establish the diagnosis in a stepwise fashion in patients aged over 50 (usually over 60) who have had symptoms for at least one or two weeks

Symptoms

Bilateral shoulder or pelvic girdle aching, or both

Morning stiffness of greater than 45 minutes' duration

Raised inflammatory response parameters (erythrocyte sedimentation rate or C reactive protein concentration)

Systemic symptoms including low grade fever, weight loss, and depression may occur

Exclude active infections, rheumatoid arthritis and other inflammatory conditions, thyroid disorders, cancer, and drugs such as statins

Basic investigations

Measure inflammatory markers (erythrocyte sedimentation rate or C reactive protein, or both)

Calcium measurements

Creatinine and urinalysis

Thyroid function test

Creatine phosphokinase measurement

Alkaline phosphatase measurement

Blood glucose measurement

Complete blood cell count with differential

Ultrasonography of the hip and shoulders, if available

Preventive health measures (optional)

Measure blood pressure

Study bone mineral density and measure 25-dehydroxyvitamin D concentrations according to regional guidelines

Test for tuberculosis (purified protein derivative (PPD) or a T cell based interferon γ release enzyme linked immunosorbent assay (ELISA), or both, with or without chest radiography) in at-risk patients

Measure cholesterol and triglyceride concentrations

Perform immunisations as appropriate for age and regional guidelines

Other screening tests including prostate specific antigen, colonoscopy, mammography as appropriate and according to regional screening recommendations

What is the histopathology of polymyalgia rheumatica?

Biopsy of the lining from shoulder joints in patients with a polymyalgic syndrome confirms synovitis in about a third of patients. The arthritis is non-erosive, unlike in rheumatoid arthritis.³⁴ The histopathology of the synovitis is non-specific, generally with predominance of CD4 positive T cells and macrophages that can produce interleukin 1 β and interleukin 6, as is also seen in the vascular infiltrate of biopsies from patients with giant cell arteritis.^{34 12}

How is polymyalgia rheumatica treated?

Unblinded uncontrolled prospective and retrospective cohort studies have shown that glucocorticosteroids

Box 2 Symptoms and markers to monitor

Morning stiffness

Proximal hip and girdle pain

Disability related to the polymyalgia rheumatica

Adverse events including osteoporotic stress fractures

Symptoms and signs suggesting an alternative diagnosis

Laboratory markers—blood glucose concentrations, erythrocyte sedimentation rate, and blood count (haemoglobin, white blood cell count, platelet count)

Bone density every one to two years

It is important to treat the patient's symptoms and not to rely exclusively on the inflammatory markers to guide treatment

are the only known effective treatment. The initial dose of prednisone is 15 mg a day, and it should be increased to no higher than 20 mg a day in the first week or two of treatment. Thereafter, the dose depends on symptom activity and the concentration of C reactive protein.^{3,4,8,13} Expert opinion recommends physiotherapy for some patients who have difficulty regaining mobility. Glucocorticosteroids are often needed for two to three years, although about 10% of patients will relapse within 10 years and require longer courses of treatment.¹⁴⁻¹⁶ If patients who are no longer taking corticosteroids have a relapse, the original dose of prednisone should be reinstated. The recommended dose of prednisone is the lowest dose that keeps symptoms in remission. Patients with chronic disease are usually maintained on as little as 2.5-5 mg prednisone daily.

It is important to tell patients about the small risk of disease recurrence at a later date in the form of giant cell arteritis without polymyalgia rheumatica.¹⁴⁻¹⁶ After the first few months of treatment, once the disease is controlled, asymptomatic patients with persistently raised inflammatory markers should not continue to be treated with high (or even higher) doses of prednisone just to reduce these markers. Persistence, for example, of a modestly raised erythrocyte sedimentation rate may have no clinical importance. It is often helpful to

determine the C reactive protein value in such cases, and if normal use this measure. A persistently or recurrently raised erythrocyte sedimentation rate may be indicative of an underlying or intercurrent disease mimic, such as a haematopoietic disorder or systemic infection.

Glucocorticosteroid related adverse events are common and include osteoporosis, avascular necrosis, infections, diabetes, insufficiency fractures, steroid myopathies, hypertension, and cataracts.^{17,18} Over-treatment with corticosteroids is often the result of underlying degenerative symptoms being misinterpreted as persistent polymyalgia rheumatica, or a persistently raised erythrocyte sedimentation rate being attributed to underlying active disease.

Management of comorbidities—including prophylaxis for cardiovascular disease and osteoporosis—is imperative. Blood pressure, blood lipids, and blood glucose should be assessed, and screening for osteoporosis should be performed at the start of treatment and throughout treatment as appropriate for the patient's age, sex, and medical history (box 2). Preventive health screening and measures—including assessment of osteoporosis—should be performed according to regional guidelines as appropriate for the patient's age, sex, and risk exposure (box 1).^{19,20} These include appropriate immunisations and tuberculosis screening in patients at risk, ideally before treatment begins. Prophylaxis for osteoporosis should be started within the first week or so of diagnosis and the start of treatment.

Non-steroidal anti-inflammatory agents have little use in the management of polymyalgia rheumatica and are associated with considerable drug related morbidity.²¹ Other alternative and adjuvant glucocorticosteroid sparing treatments that have been suggested—especially in refractory cases—include methotrexate and anti-tumour necrosis factor α agents. These compounds are of uncertain benefit in the management of polymyalgia rheumatica and are not recommended.²²⁻²⁴

ONGOING RESEARCH AND UNANSWERED QUESTIONS**Ongoing research**

A study of classification criteria for the diagnosis of polymyalgia rheumatica is in progress (American College of Rheumatology and European League Against Rheumatism). Other studies are being conducted to explore the pathogenesis and proteomic and genomic markers for diagnosis, assessment of disease activity, and response to treatment

Questions for future research

What is the aetiology of and risk factors for developing polymyalgia rheumatica?

What steroid sparing treatments are available for polymyalgia rheumatica?

What is the true spectrum of disease of polymyalgia rheumatica?

Box 3 Follow-up of polymyalgia rheumatica**Frequency of follow-up**

Weeks 1, 3, and 6 then months 3, 6, 9, and 12, with extra visits for relapses and adverse events

Treatment of relapses

For the first and second relapses, increase the prednisone to the higher dose given initially. One intramuscular injection of depo-methylprednisolone, 40-120 mg, can also be given

Further relapses

Increase the steroid dose more modestly to 1-2 mg above the previously effective dose with slow tapering, by 1 mg every one to three months, recognising that the disease may last for years. Evidence for the efficacy of steroid sparing agents such as methotrexate or anti-tumour necrosis factor α agents is poor

SUMMARY POINTS

Polymyalgia rheumatica occurs in patients who on average are over 70 years of age

Cardinal symptoms are shoulder and hip girdle pain with pronounced stiffness lasting at least one hour

Clinicians must be alert to mimics, including infection, malignancy, metabolic bone disease, and elderly onset rheumatoid arthritis

Erythrocyte sedimentation rate or C reactive protein, or both, is usually raised at disease onset

Giant cell arteritis is present in about 30% of patients

Polymyalgia rheumatica is treated with glucocorticosteroids, starting at 15 mg prednisone a day

What are the response criteria?

The core clinical response criteria include a reduction in the C reactive protein concentration or erythrocyte sedimentation rate (or both), improvement in morning stiffness, ability to raise the arms above shoulder height consistent with the patient's baseline mobility before onset of polymyalgic symptoms, and improvement in the patient's and doctor's global assessment, preferably performed on a visual analogue scale.^{9,13} Patients should be followed up regularly for at least a year (box 3).

Conclusion

Polymyalgia rheumatica is a relatively common inflammatory disease that occurs in patients over the age of 50. On average, patients are over 70 years at disease onset. The hallmark of polymyalgia rheumatica is shoulder and hip girdle pain with pronounced stiffness lasting at least one hour. Inflammatory markers, including erythrocyte sedimentation rate and C reactive protein, are almost always raised at disease onset. Mimics of polymyalgia rheumatica include malignancy, infections, metabolic bone disease, and endocrine disorders. Giant cell arteritis is seen in at least 30% of patients, and the symptoms and signs include new headache, scalp tenderness, jaw pain on chewing, and visual disturbances (which should be evaluated by temporal artery biopsy). Polymyalgia rheumatica is treated with glucocorticosteroids at an initial dose of prednisone 15 mg per day, and symptoms should improve dramatically. Drug related side effects include diabetes, hypertension, hyperlipidaemia, and osteoporosis. These side effects must be monitored and measures should be taken to prevent and manage them.

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